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[From the Laboratory of Physiology in the Harvard Medical School]

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LIKE other endosecretory glands the adrenals have been studied by removing them and by injecting their extracts. Injection experiments have shown that the substance produced by the adrenal medulla (adrenin, adrenalin, epinephrin, etc.) is capable of producing many profound bodily changes. The most important of these changes are: a cessation of the activities of the alimentary canal; a notable shifting of the circulation from the great vessels of the abdomen to the lungs, heart, limbs and central nervous system; an increased cardiac vigor; and an augmentation of the sugar content of the blood. Little attention has been paid to the important question of the possible value of these striking bodily alterations as they might occur in the natural life of animals. It is significant that these effects are caused also by nervous discharges along sympathetic pathways — the discharges that are sent forth in crises of pain and great emotion. During the past three years, in a series of investigations conducted in this laboratory,[1] we have attempted to gain insight into the meaning of the changes wrought by adrenalin or increased adrenal secretion, and in this paper I propose to discuss the bearings of our results.

Adrenalin is Liberated Normally in Fear, Rage, Asphyxia and Pain

A point of prime importance in the functioning of the adrenal medulla is its subjection to central nervous influences coming to it by way of the splanchnics. With a variety of methods, in the

[1] Cannon and de la Paz: this Journal, 1911, xxviii, p. 64. Cannon and Hoskins: *ibid.*, 1911, xxix, p. 274. Cannon, Shohl and Wright: *ibid.*, 1911, xxix, p. 280. Cannon and Lyman: *ibid.*, 1913, xxxi, p. 376. Cannon and Nice: *ibid.*, 1913, xxxii, p. 44. Gruber: *ibid.*, 1913, xxxii, pp. 221, 438; and 1914, xxxiii, p. 335.

hands of various investigators,[1] proof has been brought that artificial stimulation of the splanchnic nerves will induce secretory activity in the adrenal medulla, and that in consequence adrenalin is increased in the blood. Thus the fact is now securely established that there exists in the body a mechanism by which this endosecretory gland can be made to discharge its products promptly into the circulation.

The question whether the medulla is stimulated to activity by nervous impulses aroused by the natural events in the course of an animal's life was taken up by de la Paz and me about three years ago.[2] We found that when a cat was frightened by a barking dog the blood in the cat's vena cava close in front of the opening of the adrenal veins gave definite evidence of the presence of adrenalin (relaxation of the rhythmically contracting intestinal strip), whereas blood from the same region previous to the excitement was ineffective. Later Hoskins and I found that strong stimulation of the sciatic nerve in an anaesthetized animal—such stimulation as would cause severe pain if the animal were not anaesthetized — and also asphyxia, resulted in greater activity of the adrenal medulla, as indicated by the increased amount of adrenalin in the cava blood.[3]

Our observation on asphyxia has been supported by Borberg and Fridericia,[4] and also by Starkenstein,[5] who found that an increase of CO_2 in the blood lessens the chromaffine substance in the adrenal medulla. And recently Czubalski also has inferred, from the rise of blood-pressure in asphyxia when the adrenals are intact and the absence of the rise if the adrenals are removed, that asphyxia sets free adrenalin in the blood.[6]

[1] *See* Dreyer: this Journal, 1898–99, ii, p. 219. Tscheboksaroff: Archiv für die gesammte Physiologie, 1910, cxxxvii, p. 103. Asher: Zentralblatt für Physiologie, 1910, xxiv, p. 927. Kahn: Archiv für die gesammte Physiologie, 1911, cxl, p. 240. Meltzer and Joseph: this Journal, 1912, xxix, p. xxxiv. Elliott: Journal of physiology, 1912, xliv, p. 400. Cannon and Lyman: *Loc. cit.*, p. 377; and others.

[2] Cannon and de la Paz: *Loc. cit.*, p. 67.

[3] Cannon and Hoskins: *Loc. cit.*, p. 278.

[4] Borberg: Skandinavisches Archiv für Physiologie, 1913, xxviii, p. 125.

[5] Starkenstein: Zeitschrift für experimentelle Pathologie und Therapie, 1911, x, p. 95.

[6] Czubalski: Zentralblatt für Physiologie, 1913, xxvii, p.580.

Our observations on fear and pain have been supported by Elliott's study of the adrenalin content of the glands as affected by experimental procedures. He found that "fright," induced in cats by morphia or by β-tetrahydronaphthylamine, exhausts the glands, and that excitation of afferent nerves, such as the great sciatic, also causes adrenalin to disappear.[1] These results are what could be reasonably expected, for major emotions, as fear and rage, and such sensory stimulation as in a conscious animal would be painful are known to be accompanied by nerve impulses passing out via sympathetic fibres — impulses causing dilatation of the pupils, inhibition of gastric katastalsis and secretion, and contraction of arterioles.[2] And, as previously stated, the adrenal medulla has been proved to manifest increased secretory activity when affected by nerve impulses coming via these same pathways.

Blood Sugar is Increased in Fear, Rage, Asphyxia and Pain if the Adrenals are Intact

Artificial stimulation of splanchnic nerves not only liberates adrenalin but also releases sugar from the liver.[3] If, however, the adrenals are removed from the body, splanchnic stimulation will not evoke glycosuria.[4] The participation of the adrenal medulla, therefore, seems to be essential for the mobilization of sugar in the blood, when that is accomplished by nerve impulses.

As pointed out above, adrenal secretion is increased in major emotional states, in asphyxia, and on stimulation of nerves for pain; hyperglycaemia is the normal accompaniment of such experimental nervous stimulations as evoke an increased adrenal secretion; therefore, that fear and rage, pain and asphyxia would give rise to hyperglycaemia might reasonably be expected.

[1] ELLIOTT: *Loc. cit.*, p. 409.

[2] *See* CANNON: The Mechanical Factors of Digestion, London and New York, 1911, p. 217; also American journal of the medical sciences, 1909, cxxxvii, p. 480.

[3] *See* MACLEOD: Diabetes: its Pathological Physiology, London, 1913, pp. 61–62.

[4] *See* GAUTRELET and THOMAS: Comptes rendus de la Société de Biologie, 1909, lxvii, p. 233. MACLEOD: Proceedings of the Society for Experimental Biology and Medicine, 1911, viii, p. 110.

The influence of asphyxia as a highly potent condition for the mobilization of sugar in the blood is well established.[1] Starkenstein has shown, however, that asphyxia due to carbon monoxide poisoning is not accompanied by hyperglycaemia if the adrenal glands have been removed.[2]

That experimental procedures attended by pain result in the appearance of sugar in the urine was demonstrated many years ago by Böhm and Hoffman.[3] Their observations on cats have proved true also of rabbits;[4] and recently it has been shown that an operation involving some pain increases blood sugar in dogs.[5]

That pure emotional excitement — fear or rage — will have the same effect was proved when Shohl, Wright and I obtained glycosuria in cats by fastening them to a comfortable holder or by placing them in small cages and permitting a dog to bark at them. Whether glycosuria appeared promptly or not depended on the animal's emotional reaction to its experience. Neither pain, cooling nor being bound, therefore, was a factor in the result — the essential element was the fright or rage of the animal.[6] Our conclusion has been confirmed by one of my former students, Dr. W. G. Smillie, who found that 4 of 9 medical students (all normally aglycosuric) had glycosuria after a hard examination, and only 1 of the 9 had glycosuria after an easier examination.[7] Also Rolly and Opper-

[1] For evidence and for reference to literature, *see* BANG: Der Blutzucker, Wiesbaden, 1913, pp. 104–108.

[2] STARKENSTEIN: *Loc. cit.*, p. 94. He was able to produce glycosuria in the absence of the adrenals by strong stimulation of the central end of the cut vagus; he therefore concluded that the sympathetic impulses are primary and that the adrenals are accessory in evoking glycogenolysis.

[3] BÖHM and HOFFMAN: Archiv für experimentelle Pathologie und Pharmakologie, 1878, viii, p. 295.

[4] ECKHARD: Zeitschrift für Biologie, 1903, xliv, p. 408.

[5] LOEWY and ROSENBERG: Biochemische Zeitschrift, 1913, lvi, p. 114.

[6] CANNON, SHOHL and WRIGHT: *Loc. cit.*, p. 283.

[7] The tests, which were positive with Fehling's solution, Nylander's reagent, and also with phenyl-hydrazine, were made on the first urine passed after the examination. Mr. C. H. Fiske and I have found sugar in the urine in 12 of 25 members of the Harvard University foot-ball squad, immediately after the final and most exciting contest of the season. Five of the positive cases were substitutes who were not called upon to enter the game. The only spectator whose urine was examined had a marked glycosuria.

mann, Jacobsen, and Hirsch and Reinbach have recently reported that the mere handling of a rabbit preparatory to operating on it will increase the blood sugar (in some cases from .10 to .23 and .27 per cent) and may result in glycosuria.[1] Indeed, the readiness with which this response occurs has been pointed out as a source of error in estimates of the "normal" sugar content of the blood.

In our studies[2] we observed that animals which had glycosuria when bound for about an hour, failed to have it after careful adrenalectomy, although bound between two and three times as long as before, and although still manifesting the same degree of excitement which they had manifested previous to the operation. This result harmonizes with that already reported that the presence of the adrenals is necessary when hyperglycaemia is to be produced by splanchnic stimulation.

Fear, rage, asphyxia and pain, therefore, are accompanied by an increased discharge of adrenalin into the blood, and by a freeing of stored glycogen from the liver for circulation through the body as glucose. The hyperglycaemia and the adrenalinaemia are both due to nervous discharges. Since, in the absence of the adrenals, nerve impulses fail to evoke sugar; and since, in the absence of nerve impulses, a sufficient injection of adrenalin will evoke sugar, the inference seems justified that, for the ready increase of blood sugar by nervous discharges in emotions, circulating adrenalin must be simultaneously increased. What explanation can be offered for this remarkable outpouring from the adrenal medulla and the concomitant glycogenolysis that floods the body with sugar?

The Reflex Nature of Bodily Responses to Pain and the Major Emotions

The most significant feature of these bodily reactions to pain and to emotion-provoking objects is that they are of the nature of reflexes, — they are not willed movements, indeed they are often distressingly beyond the control of the will. The pattern of the

[1] Rolly and Oppermann: Biochemische Zeitschrift, 1913, xlix, p. 201. Jacobsen: *ibid.*, 1913, li, p. 449. Hirsch and Reinbach: Zeitschrift für physiologische Chemie, 1913, lxxxvii, p. 122.

[2] Cannon, Shohl and Wright: *Loc. cit.*, p. 285.

reaction, in these as in other reflexes, is deeply inwrought in the workings of the nervous system, and when the appropriate occasion arises, typical organic responses are evoked through inherent automatisms.

It has long been recognized that the most characteristic feature of reflexes is their "purposive" nature, or their utility either in preserving the welfare of the organism or in safeguarding it against injury. The reflexes of sucking, swallowing, vomiting and coughing, for instance, need only to be mentioned to indicate the variety of ways in which reflexes favor the continuance of existence. When, therefore, these automatic responses accompanying pain and fear and rage — the increased discharge of adrenalin and sugar — are under consideration, it is reasonable to enquire first as to their utility.

Numerous ingenious suggestions have been offered to account for the more obvious changes accompanying emotional states — as, for example, the bristling of the hair and the uncovering of the teeth in an access of rage.[1] The most widely applicable explanation proposed for these spontaneous reactions is that during the long course of racial experience they have been developed for quick service in the struggle for existence. McDougall has suggested that an association has become established between peculiar emotions and these ingrained native reactions; thus the emotion of fear is associated with the instinct for flight, and the emotion of anger or rage with the instinct for fighting or attack.[2] Crile likewise has emphasized the importance of adaptation and natural selection, operative through age-long racial experience, in enabling us to account for the already channelled responses which we find established in our nervous organization. And on a principle of "phylogenetic association" he assumes that fear, born of innumerable injuries in the course of evolution, has developed into portentous foreshadowing of possible injury and has become, therefore, capable of arousing in the body all the offensive and defensive activities that favor the survival of the organism.[3]

[1] *See* DARWIN: Expression of Emotions in Man and Animals, New York, 1905, pp. 101, 117.

[2] MCDOUGALL: Introduction to Social Psychology, London, 1908, pp. 49, 59.

[3] CRILE: Boston medical and surgical journal, 1910, clxiii, p. 893.

Because the adrenalinaemia and the hyperglycaemia following painful or strong emotional experiences are reflex in character, and because reflexes as a rule are useful responses, we are justified in the assumption that under these circumstances the increase of adrenalin and sugar in the blood is useful. What then is the possible value of these reactions?

The Utility of Sugar and Adrenalin Liberated in Pain and the Major Emotions

That the outpouring of adrenalin and sugar in conditions of pain and the major emotions has value for the organism was the leading idea in the researches recently reported from this laboratory.[1] In order that these reactions may be useful they must be *prompt.* Such is the case. Some unpublished observations made in this laboratory show that the latent period of adrenal secretion, when the splanchnic nerve is stimulated below the diaphragm, is not longer than 16 seconds; and Macleod states that within a few minutes after splanchnic stimulation the sugar in the blood rises between 10 and 30 per cent.[2] The two secretions are, therefore, almost instantly ready for service.

Conceivably the two secretions might act in conjunction or each might have its own function alone. Thus adrenalin might serve in co-operation with nervous excitement to produce hyperglycaemia, or it might have that function and other functions quite apart from that. Before these possibilities are considered, however, the value of the hyperglycaemia itself will be discussed.

The Utility of Increased Blood Sugar. — In the paper on emotional glycosuria previously mentioned,[3] a clue was taken from McDougall's suggestion of a relation between "flight instinct" and "fear emotion," and "pugnacity instinct" and "anger emotion." And the point was made that, since the fear emotion and the anger emotion are, in wild life, likely to be followed by activities (running or fighting) which require contraction of great muscular masses in supreme and prolonged struggle, a mobilization of sugar

[1] *See* CANNON: Proceedings American Philosophical Society, 1911, l, p. 227.
[2] MACLEOD: Diabetes, etc., p. 80.
[3] CANNON, SHOHL and WRIGHT: *Loc. cit.*, p. 286.

in the blood might be of signal service to the laboring muscles. Pain — and fighting is almost certain to involve pain — would, if possible, call forth even greater muscular effort. "In the agony of pain almost every muscle of the body is brought into strong action," Darwin wrote, for "great pain urges all animals, and has urged them during endless generations, to make the most violent and diversified efforts to escape from the cause of suffering."[1]

That muscular work is performed by energy supplied in carbonaceous material is shown by the great increase of carbon-dioxide output in severe muscular work, which may exceed twenty times the output during rest. Furthermore, the storage of glycogen in muscle, and the disappearance of this glycogen deposit from excised muscle stimulated to activity,[2] or its reduction after excessive contractions produced by strychnine,[3] and the lessened ability of muscles to work if their glycogen store has been reduced,[4] and the simple chemical relation between sugar and the lactic acid which appears when muscles are repeatedly made to contract, are all indications that carbohydrate (sugar and glycogen) is the elective source of energy for contraction. This conclusion is supported in recent careful studies by Benedict and Cathcart, who have shown that a small but distinct increase in the respiratory quotient occurs during muscular work, and that a decrease in the quotient follows, thus pointing to a larger proportion of carbohydrate burned during muscular work than before or after — i.e., a call on the carbohydrate deposits of the body.[5]

[1] Darwin: *Loc. cit.*, p. 72. It is recognized that both pain and the major emotions may have at times depressive rather than stimulating effects. Though severe pain may soon induce extreme prostration, the whip and spur illustrate its primary exciting action. And though fear may become the most depressing of all emotions, it acts at first as a powerful stimulus. "A man or animal driven through terror to desperation is endowed with wonderful strength, and is notoriously dangerous in the highest degree." (Darwin: *Loc. cit.*, p. 81.)

[2] Nasse: Archiv für die gesammte Physiologie, 1869, ii, p. 106; 1877, xiv, p. 483.

[3] Frentzel: Archiv für die gesammte Physiologie, 1894, lvi, p. 280.

[4] Zuntz: Oppenheimer's Handbuch der Biochemie, Jena, 1911, iv (first half), p. 841.

[5] Benedict and Cathcart: Muscular Work, a metabolic study, Washington, 1913, pp. 85–87.

Whether circulating sugar can be immediately utilized by active muscles has been a subject of dispute. The claim of Chauveau and Kaufmann that a muscle uses about three and a half times as much blood sugar when active as when resting,[1] although supported by Quinquaud,[2] and by Morat and Dufourt,[3] has been denied by Pavy, who failed to find any difference between the sugar content of arterial and venous blood when the muscle was contracting;[4] and also by Magnus-Levy, who has estimated that the amount of change in sugar content of the blood passing through a muscle must be so slight as to be within the limits of the error of analysis.[5] On the other hand, when blood or Ringer's solution is repeatedly perfused through contracting heart muscle, the evidence is clear that the contained sugar may more or less completely disappear. Thus Locke and Rosenheim found that from 5 to 10 centigrams of dextrose disappeared from Ringer's solution repeatedly circulated through the rabbit heart for eight or nine hours.[6] And recently Patterson and Starling have shown that if blood is perfused repeatedly through a heart-lung preparation for three or four hours, and the heart is continually stimulated by adrenalin added to the blood, the sugar in the blood wholly vanishes; or if the supply of sugar is maintained, the consumption may rise as high as 8 mgms. per gram per hour — about four times the usual consumption.[7] When an animal is eviscerated it may be regarded as a preparation in which the muscles are perfused with their proper blood, pumped by the heart and oxygenated by the lungs. Under these circumstances, the percentage of sugar in the blood steadily falls,[8] because the utilization by the tissues is not

[1] Chauveau and Kaufmann: Comptes rendus, Académie des Sciences, 1886, ciii, p. 1062.

[2] Quinquaud: Comptes rendus, Société de Biologie, 1886, xxxviii, p. 410.

[3] Morat and Dufourt: Archives de physiologie, 1892, xxiv, p. 327.

[4] Pavy: The Physiology of the Carbohydrates, London, 1894, p. 166.

[5] Magnus-Levy: v. Noorden's Handbuch der Pathologie des Stoffwechsels, 1906, i, p. 385.

[6] Locke and Rosenheim: Journal of physiology, 1907, xxxvi, p. 211.

[7] Patterson and Starling: Journal of physiology, 1913, xlvii, p. 143.

[8] *See* Macleod and Pearce: this Journal, 1913, xxxii, p. 192. Pavy and Siau: Journal of physiology, 1903, xxix, p. 375. Macleod: this Journal, 1909, xxiii, p. 278.

compensated for by further supply from the liver. Thus, although there may be doubt that analyses of sugar in the blood flowing into and out from an active muscle during a brief period can be accurate enough to prove a clear difference, the evidence from the experiments above cited shows that when the supply of sugar is limited it disappears to a greater or less degree when passed repeatedly through muscular organs.

The argument may be advanced, of course, that the sugar which thus disappears is not directly utilized, but must first be changed to glycogen. There is little basis for this assumption. There is, however, considerable evidence that increasing blood sugar does, in fact, directly increase muscular efficiency. Thus Locke proved that if oxygenated salt solution is perfused through the rabbit heart, the beats begin to weaken after one or two hours; but if now 0.1 per cent dextrose is added to the perfusing fluid the beats at once become markedly stronger and may continue with very slow lessening of strength as long as seven hours.[1] And Schumberg noted that when he performed a large amount of general bodily work (thus using up blood sugar) and then tested flexion of the middle finger in an ergograph, the ability of the muscle was greater if he drank a sugar solution than if he drank an equally sweet solution of "dulcin." He did not know during the experiment which solution he was drinking.[2] These observations have been confirmed by Prantner and Stowasser, and by Frentzel.[3] In experiments on cats Lee and Harrold found that when sugar is removed from the animal by means of phlorhizin the tibialis anticus is quickly fatigued; but if, after the phlorhizin treatment, the animal is given an abundance of sugar and then submitted to the test, the muscle shows a much larger capacity for work.[4] All this evidence is, of course, favorable to the view that circulating sugar may be quickly utilized by contracting muscles.

From experimental results presented above it is clear that muscles work preferably by utilizing the energy stored in sugar, that great muscular labor is capable of considerably reducing the

[1] Locke: Centralblatt für Physiologie, 1900, xiv, p. 671.

[2] Schumberg: Archiv für Physiologie, 1896, p. 537.

[3] Frentzel: Archiv für Physiologie, 1899, Supplement Band, p. 145.

[4] Lee and Harrold: this Journal, 1900, iv, p. ix.

quantity of stored glycogen and of circulating sugar, and that under circumstances of a lessened sugar content the increase of blood sugar considerably augments the ability of muscles to continue contracting. The conclusion seems justified, therefore, that the hyperglycaemia attendant on the major emotions and pain would be of direct benefit to the organism in the strenuous muscular efforts involved in flight or conflict or struggle to be free.

The Utility of Increased Adrenalin in the Blood. — In early work on the effects of removal of the adrenal bodies, muscular weakness was not infrequently noted. In 1892 Albanese showed that muscles stimulated after adrenalectomy were much more exhausted than when stimulated the same length of time in the same animal before the removal.[1] Similarly Boinet reported that rats recently deprived of their adrenal glands were much more quickly exhausted in a revolving cage than were normal animals.[2] A beneficial effect of adrenal extract on fatigued muscle, even when applied to the solution in which the isolated muscle is contracting, was claimed by Dessy and Grandis, who studied the phenomenon in the salamander.[3]

It seemed possible, because of the early evidence that adrenalectomy has a debilitating effect on muscular power, and that injection of adrenal extract has an invigorating effect, that increased adrenal secretion, as a reflex result of pain or the major emotions, might not only be useful in helping to mobilize sugar, but also might act in itself as a dynamogenic factor in the performance of muscular work. On the basis of this possibility Nice and I tested the effect of stimulating the left splanchnic nerve (thus causing adrenal secretion), or injecting adrenalin, on the contraction of the fatigued tibialis anticus.[4] We found that when

[1] Albanese: Archives italiennes de biologie, 1892, xvii, p. 243.

[2] Boinet: Comptes rendus, Société de Biologie, 1895, xlvii, pp. 273, 498.

[3] Dessy and Grandis: Archives italiennes de biologie, 1904, xli, p. 231. Biedl's observation (*See* Biedl: Innere Sekretion, Second Edition, Leipzig, 1913, i, p. 376), that in selachians removal of the interrenal bodies (corresponding to the adrenal cortex) results in muscular weakness, might indicate that the cortex was directly involved in muscular efficiency, but the failure of the animals to take food after undergoing the operation renders that conclusion hazardous.

[4] Cannon and Nice: *Loc. cit.*, p. 54.

arterial pressure was of normal height, and was prevented from rising in the legs while the splanchnic was being stimulated, there was a distinct rise in the height of contraction of the fatigued muscle. We drew the inference that adrenalin set free in the blood may operate favorably to the organism by preparing fatigued muscles for better response to the nervous discharges sent forth in great excitement.

This inference has been further tested during the past summer by one of my students, Mr. C. M. Gruber, who has examined the effects of minute amounts of adrenalin (0.1 or 0.5 cc. of 1:100,000), and also of splanchnic stimulation, on the threshold stimulus of fatigued neuromuscular and muscular apparatus. Fatigue raises the threshold not uncommonly 100 or 200 per cent and in some instances as much as 600 per cent. Rest will restore the normal threshold in periods varying from 15 to 120 minutes, according to the length of previous stimulation. If a small dose of adrenalin is given, however, the normal threshold may be restored in 3 to 5 minutes.[1]

From the foregoing evidence the conclusion is warranted that adrenalin, when freely liberated in the blood, not only aids in bringing out sugar from the liver's store of glycogen, but also has a remarkable influence in quickly restoring to fatigued muscles, which have lost their original irritability, the same readiness for response which they had when fresh. Thus the adrenalin set free in pain and in fear and rage would put the muscles of the body unqualifiedly at the disposal of the nervous system; the difficulty which nerve impulses might have in calling the muscles into full activity would be practically abolished; and this provision, along with the abundance of energy-supplying sugar newly flushed into the blood, would give to the animal in which these mechanisms are most efficient the best possible conditions for putting forth supreme muscular efforts.[2]

Does Adrenalin Normally Secreted Inhibit the Use of Sugar

[1] *See* GRUBER: this Journal, 1914, xxxiii, p. 354.

[2] If these results of emotion and pain are not "worked off" by action, it is conceivable that the excessive adrenalin and sugar in the blood may have pathological effects (*Cf.* CANNON: Journal of the American Medical Association, 1911, lvi, p. 742).

by the Tissue? — The only evidence opposed to the conclusion which has just been drawn is that which may be found in results recently reported by Wilenko. He injected adrenalin into urethanized rabbits, usually 1 mgm. per kilo body weight, and then found that the animals did not oxidize any part of an intravenous injection of glucose. Rabbits supplied with glucose in a similar manner, but not given adrenalin, have an increased respiratory quotient. Wilenko concluded therefore that adrenalin lessens the capacity of the organism to burn carbohydrates.[1] In a later paper he reported that adrenalin when added to Locke's solution (with glucose), and perfused through the isolated rabbit heart, notably increases the use of sugar by the heart (from 2.2–2.8 to 2.9–4.3 mgm. glucose per gm. heart muscle per hour), but that the heart removed after the animal had received a subcutaneous injection of adrenalin uses much less sugar, only 0.5–1.2 mgm. per gm. per hour. From these results Wilenko concludes that adrenalin glycosuria is the result of the disturbance of the *use* of sugar — an effect which is not direct on the sugar-consuming organ, but indirect through action on some other organ.[2]

Wilenko's conclusion fails to account readily for the disappearance of glycogen from the liver in adrenalin glycosuria. Furthermore, Lusk has recently reported that the subcutaneous administration of adrenalin (1 mgm. per kilo body weight) to dogs, simultaneously with 50 grams of glucose by mouth, interferes not at all with the use of the sugar — the respiratory quotient remains for several hours at 1.0; i.e., at the figure which glucose alone would have given.[3] In other words Lusk's results with dogs are directly contradictory to Wilenko's results with rabbits. Nevertheless, Wilenko's conclusion might be quite true for the glycosuria produced by adrenalin alone (which must be excessive), and yet have no bearing whatever on the glycosuria produced physiologically by splanchnic stimulation, even though some adrenalin is thereby simultaneously liberated.

[1] Wilenko: Biochemische Zeitschrift, 1912, xlii, p. 58.

[2] Wilenko: Archiv für experimentelle Pathologie und Pharmakologie, 1913, lxxi, p. 266.

[3] Lusk: Proceedings of the Society for Experimental Biology and Medicine, 1914, xi, p. 49.

The amount of adrenalin injected to produce adrenalin glycosuria is enormous. Mr. H. Osgood has studied in this laboratory the effects on blood pressure of alternately stimulating the left splanchnic nerve (with the splanchnic vascular area eliminated) and injecting adrenalin, and by this method[1] has shown that the amount secreted after five seconds of stimulation varies between 0.0015 and 0.007 mgm. If 0.005 mgm. is taken as rather high average figure, and doubled (for the two glands), the amount would be 0.01 mgm. To produce adrenalin glycosuria an animal weighing 2 kilos would be injected with two hundred times this amount. It is granted that more adrenalin would be secreted if the nerves were stimulated longer than five seconds, and that with subcutaneous or intraperitoneal injection (to produce glycosuria), the amount of adrenalin in the blood at one time would not be so great as if the injection were intravenous; but even with these concessions the amount of adrenalin in the blood needed to produce glycosuria is probably much above the amount following physiological stimulation of the glands.

Other evidence that the amount of adrenalin discharged when the glands are stimulated is not so great as the amount needed to produce glycosuria when acting alone is presented in experiments by Macleod. He found that if the nerve fibres to the liver were destroyed, stimulation of the splanchnic, which would cause increased adrenal secretion, did not increase the blood sugar. The hyperglycaemia due to splanchnic stimulation, therefore, is a nervous effect, dependent, to be sure, on the presence of adrenalin in the blood, but the amount of adrenalin present is not in itself capable of evoking the hyperglycaemia.[2]

Furthermore, the hyperglycaemia following splanchnic stimulation may long outlast the stimulation period. The adrenals, however, as has been demonstrated by Osgood in this laboratory, are soon fatigued, and fail to respond to repeated stimulation. They seem to be incapable of prolonged action.

Again, as Macleod has shown, hyperglycaemia can be induced, if the adrenals are intact, merely by stimulating the nerves going to the liver.[3] The hyperglycaemia of splanchnic origin, therefore,

[1] *See* Elliott: Journal of physiology, 1912, xliv, p. 376.

[2] Macleod: Diabetes, etc., pp. 64–73. [3] Macleod: Diabetes, etc., pp. 68–72.

is not due to a disturbance of the *use* of sugar in the body, as Wilenko claims for the hyperglycaemia after adrenalin injection, but is a result of a hyperglycogenolysis of nervous origin.

We may conclude therefore that since the conditions of Wilenko's observations are not comparable with emotional conditions, his inferences are not pertinent to the present discussion; that when both adrenalin and sugar are increased in the blood as a result of excitement, the hyperglycaemia is not due to adrenalin inhibiting the use of sugar by the tissues, and that there is no evidence at present to show that the brief augmentation of adrenal discharge, following excitement or splanchnic stimulation, affects in any deleterious manner the utilization of sugar as a source of energy. Indeed, the observation of Wilenko and of Patterson and Starling, above mentioned, that adrenalin increases the use of sugar by the heart, may signify that a physiological discharge of the adrenals can have a favorable rather than an unfavorable effect on the employment of sugar by the tissues.

The Vascular Changes Produced by Adrenalin are Favorable to Great Muscular Exertion

Quite in harmony with the foregoing argument that sugar and adrenalin, which are poured into the blood during emotional excitement, render the organism more efficient in the physical struggle for existence, are the vascular changes wrought by increased adrenalin, probably in co-operation with sympathetic innervations. Through oncometric studies, Oliver and Schäfer proved that the viscera of the splanchnic area — as the spleen, the kidneys and the intestines — suffer a considerable diminution of volume when adrenalin is administered, whereas the limbs into which the blood is forced from the splanchnic region actually increase in size.[1] In other words, at times of stress blood may be driven out of vegetative organs of the interior, which serve the routine needs of the body, into the skeletal muscles, which have to meet by extra action the urgent demands of conflict.

But there are exceptions to the statement that by adrenalin the viscera are emptied of their blood. It is well known that adrenalin

[1] Oliver and Schäfer: Journal of physiology, 1895, xviii, p. 240.

has a vasodilator, not a vasoconstrictor, effect on the arteries of the heart; it is well known also that adrenalin affects the intracranial and the pulmonary vessels only slightly, if at all.[1]

Thus the absolutely essential organs — the "tripod of life" — the heart, lungs and brain (as well as the skeletal muscles) — are, in times of excitement, when the adrenal glands discharge, abundantly supplied with blood taken from organs of less importance in critical moments.

The Muscles May Help Themselves by Operating the Adrenal Mechanism

As previously stated, Hoskins and I have shown that asphyxia causes an augmented secretion of adrenalin.[2] Asphyxia is a long recognized method of inducing hyperglycaemia. Hoskins and McClure, in extension of the theory which has underlain the researches summarized in this paper, have suggested that excessive muscular activity, such as might attend flight or conflict, would lead to partial asphyxia, and that this condition would naturally act in conjunction with emotional excitement and pain to bring forth a still greater adrenal discharge and a still greater output of sugar from the liver. And these in turn would serve the laboring muscles in the manner already described.[3] This suggestion is in accord with Macleod's that the increased glycogenolysis produced by muscular exercise is possibly associated with increased carbon dioxide in the blood.[4] And it also harmonizes with Zuntz's statement that the asphyxia of great physical exertion may call out sugar to such a degree that, in spite of the increased use of it in the active muscles, glycosuria may ensue.[5]

Conclusion

To what extent the slight constant secretion of the adrenal glands serves the organism is not yet well determined. As several observers have shown, the first effect of injecting small amounts

[1] *See* Biedl: *Loc. cit.*, pp. 434, 435.
[2] Cannon and Hoskins: *Loc. cit.*, p. 275.
[3] Hoskins and McClure: Archives of internal medicine, 1912, x, p. 355.
[4] Macleod: Diabetes, etc., p. 184. [5] Zuntz: *Loc. cit.*, p. 854.

of adrenalin into carnivorous animals is to lower blood pressure.[1] Adrenal secretion cannot be, therefore, at least among the carnivora, a direct factor in maintaining the normal high tonus of the vasomotor system. It is probable, however, that incredibly minute amounts of this substance in the circulating blood somehow sensitize the myoneural junctions of the sympathetic system, and thus aid the nervous action.[2] Such quiet service, however, is quite distinct from the profound changes in the organism which larger amounts of adrenalin are capable of provoking or helping to provoke.

The cessation of activities of the alimentary canal (thus freeing energy for other parts); the shifting of the blood from the less insistent abdominal viscera to the organs immediately essential to life itself, such as the lungs, the heart, the central nervous system and, at critical moments, the skeletal muscles as well; the increased cardiac vigor; the quick abolition of the effects of muscular fatigue, the mobilizing of energy-giving sugar in the circulation — these are the changes which occur when fear or rage or pain causes the adrenal glands to pour forth an excessive secretion. These changes in the body are, each one of them, *directly serviceable in making the organism more efficient in the struggle which fear or rage or pain may involve;* for fear and rage are organic preparations for action, and pain is the most powerful known stimulus to supreme exertion. The organism which with the aid of increased adrenal secretion can best muster its energies, can best call forth sugar to supply the laboring muscles, can best lessen fatigue, and can best send blood to the parts essential in the run or the fight for life, is most likely to survive. Such, according to the view here propounded, is the function of the adrenal medulla at times of great emergency.[3]

[1] *See* Hoskins and McClure: *Loc. cit.*, p. 353. Cannon and Lyman: *Loc. cit.* p. 376. [2] *Cf.* Elliott: Journal of physiology, 1904, xxxi, p. xx.

[3] Since this paper was prepared Dr. W. L. Mendenhall and I have found that splanchnic stimulation may greatly hasten the coagulation of the blood. This result does not occur if the adrenal gland has been removed on the side stimulated. Thus excitement and pain, through the agency of the adrenal medulla, may be serviceable to the organism in preventing loss of blood in case of vascular injury. The pertinence of these observations to the view presented in this paper is obvious.

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